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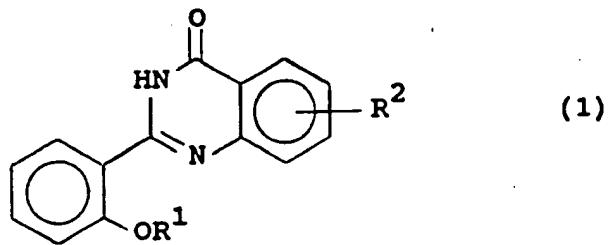
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㉓ Quinazolinone derivatives.

㉔ Compounds of the formula (1):



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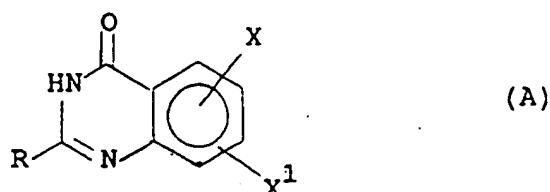
and pharmaceutically acceptable salts thereof are described wherein R¹ is C₁-₆alkyl, C₂-₆alkenyl, C₃-₅cycloalkyl/C₁-₄alkyl, phenyl/C₁-₄alkyl or C₁-₄alkyl substituted by 1 to 6 fluoro groups; R² is hydrogen, C₁-₆alkyl, C₁-₆alkylthio, C₁-₆alkoxy, nitro or -NR³R⁴; and R³ and R⁴ are independently hydrogen or C₁-₄alkyl optionally substituted by hydroxy provided that the carbon atom adjacent to the nitrogen atom is not substituted by hydroxy; with the proviso that R¹ is not methyl or ethyl when R² is hydrogen. Processes for their preparation, pharmaceutical compositions containing them and their use as medicaments are described.

CHEMICAL COMPOUNDS

The present invention relates to quinazolinone derivatives. This invention further relates to processes for their preparation, their use as therapeutic agents and to pharmaceutical compositions containing them. The compounds of this invention are inhibitors of a calmodulin insensitive cyclic GMP phosphodiesterase and are of use in combatting conditions where such inhibition is thought to be beneficial. They are bronchodilators and are therefore of use in combatting chronic reversible obstructive lung diseases such as asthma and bronchitis. Furthermore they are vasodilators and are therefore of value in combatting angina, hypertension and congestive heart failure.

Japanese Patent Application No. 52-51378 discloses compounds of the general formula (A) :

10

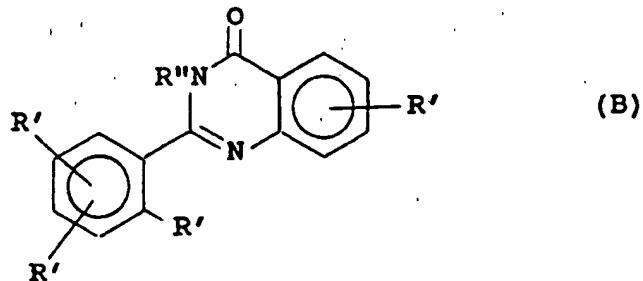


15

wherein R is an alkyl, styryl, lower alkoxy, nitro, halo or a substituted phenyl group, and X and X^1 which may be the same or different are hydrogen, halo, nitro or lower alkyl. These compounds are described as being of value as pharmaceutical products such as bactericidal and miticidal agents or as intermediates in the synthesis thereof. 2-(2-Ethoxyphenyl)quinazolin-4(3H)-one is specifically disclosed.

US Patent 3169129 discloses compounds of the general formula (B) :

25



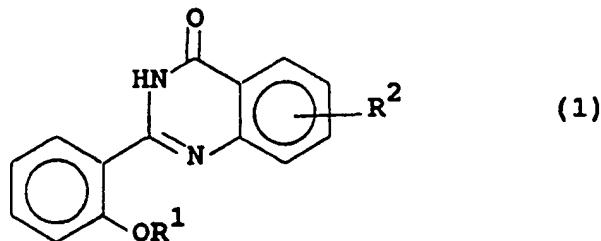
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wherein R' represents hydrogen or a substituent such as halogen, hydroxy, $\text{C}_1\text{--4}$ alkyl or $\text{C}_1\text{--4}$ alkoxy and R'' is hydrogen or $\text{C}_1\text{--4}$ alkyl. These compounds are described as having useful fluorescent properties. Although 2-(2-methoxyphenyl)quinazolin-4(3H)-one is specifically disclosed, there is no suggestion of pharmacological activity.

According to the present invention there is provided compounds of the formula (1) :

40

45



50

and pharmaceutically acceptable salts thereof, wherein
 R^1 is $\text{C}_1\text{--6}$ alkyl, $\text{C}_2\text{--6}$ alkenyl, $\text{C}_3\text{--5}$ cycloalkyl $\text{C}_1\text{--4}$ alkyl, phenyl $\text{C}_1\text{--4}$ alkyl or $\text{C}_1\text{--4}$ alkyl substituted by 1 to 6 fluoro groups;
 R^2 is hydrogen, $\text{C}_1\text{--6}$ alkyl, $\text{C}_1\text{--6}$ alkylthio, $\text{C}_1\text{--6}$ alkoxy, nitro or $-\text{NR}^3\text{R}^4$; and

R^3 and R^4 are independently hydrogen or C_1 - C_4 alkyl optionally substituted by hydroxy provided that the carbon atom adjacent to the nitrogen atom is not substituted by hydroxy; with the proviso that R^1 is not methyl or ethyl when R^2 is hydrogen.

Suitably R^1 is C_2 - C_5 alkyl for example ethyl, n-propyl, isopropyl, butyl, isobutyl or pentyl.

5 Suitably R^1 is C_3 - C_5 alkenyl for example allyl, butenyl or pentenyl.

Suitably R^1 is cyclopropylmethyl or benzyl.

Examples of C_1 - C_4 alkyl substituted by 1 to 6 fluoro groups include $-CF_3$, $-CH_2CF_3$ or $-CF_2CHFCF_3$.

Preferably R^1 is n-propyl.

Suitably R^2 is hydrogen or C_1 - C_6 alkyl for example methyl or ethyl.

10 Suitably R^2 is C_1 - C_6 alkylthio or C_1 - C_6 alkoxy for example methylthio, ethylthio, methoxy or ethoxy.

Suitably R^2 is nitro or $-NR^3R^4$ for example methylamino, dimethylamino or 2-hydroxyethylamino.

Particular compounds of this invention are :

2-(2-propoxyphenyl)quinazolin-4(3H)-one,

7-methylthio-2-(2-propoxyphenyl)quinazolin-4(3H)-one,

15 7-nitro-2-(2-propoxyphenyl)-4(3H)-quinazolinone,

7-amino-2-(2-propoxyphenyl)-4(3H)-quinazolinone, or

7-methylamino-2-(2-propoxyphenyl)-4(3H)-quinazolinone

or pharmaceutically acceptable salts thereof.

This invention covers all tautomeric and optical isomeric forms of compounds of formula (1).

20 Compounds of the formula (1) may form pharmaceutically acceptable salts with metal ions, such as alkali metals for example sodium and potassium, or with an ammonium ion.

Compounds of the formula (1') wherein R^2 is $-NR^3R^4$ may form pharmaceutically acceptable salts with acids such as hydrochloric, hydrobromic, sulphuric and phosphoric acids.

25 In order to use a compound of the formula (1) or a pharmaceutically acceptable salt thereof for the treatment of humans and other mammals it is normally formulated in accordance with standard pharmaceutical practice as a pharmaceutical composition.

Compounds of formula (1) and their pharmaceutically acceptable salts may be administered in standard manner for the treatment of the indicated diseases, for example orally, sublingually, parenterally, transdermally, rectally, via inhalation or via buccal administration.

30 Compounds of formula (1) and their pharmaceutically acceptable salts which are active when given orally or via buccal administration can be formulated appropriately in dosage forms such as liquids, syrups, tablets, capsules and lozenges. An oral liquid formulation will generally consist of a suspension or solution of the compound or salt in a liquid carrier for example, ethanol, glycerine or water with a flavouring or colouring agent. Where the composition is in the form of a tablet, any pharmaceutical carrier routinely used

35 for preparing solid formulations may be used. Examples of such carriers include starch, celluloses, lactose, sucrose and magnesium stearate. Where the composition is in the form of a capsule, any routine encapsulation process may be suitable, for example using the aforementioned carriers in a hard gelatin capsule shell. Where the composition is in the form of a soft gelatin shell capsule, any pharmaceutical carrier routinely used for preparing dispersions or suspensions may be considered, for example aqueous

40 gums, celluloses, silicates or oils and are incorporated in a soft gelatin capsule shell.

Typical parenteral compositions consist of a solution or suspension of the compound or salt in a sterile aqueous or non-aqueous carrier optionally containing a parenterally acceptable oil or solubilising agent, for example polyethylene glycol, polyvinylpyrrolidone, 2-pyrrolidone, cyclodextrin, lecithin, arachis oil or sesame oil.

45 A typical suppository formulation comprises a compound of formula (1) or a pharmaceutically acceptable salt thereof which is active when administered in this way, with a binding and/or lubricating agent, for example polymeric glycols, gelatins, cocoa-butter or other low melting vegetable waxes or fats or their synthetic analogues.

Typical transdermal formulations comprise a conventional aqueous or non-aqueous vehicle, for example 50 a cream, ointment, lotion or paste or are in the form of a medicated plaster, patch or membrane.

Typical compositions for inhalation are in the form of a solution, suspension or emulsion that may be administered in the form of an aerosol using a conventional propellant such as dichlorodifluoromethane or trichlorofluoromethane, or are in the form of a powder for insufflation.

55 Preferably the composition is in unit dosage form, for example a tablet, capsule or metered aerosol dose, so that the patient may administer to himself a single dose.

Each dosage unit for oral administration contains suitably from 0.001 mg/Kg to 30 mg/Kg, and preferably from 0.005 mg/Kg to 15 mg/Kg, and each dosage unit for parenteral administration contains suitably from 0.001 mg/Kg to 10 mg/Kg, of a compound of formula (1) or a pharmaceutically acceptable salt

thereof calculated as the free base.

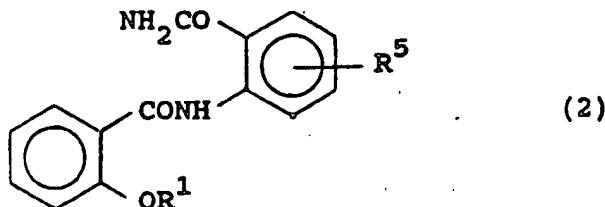
The daily dosage regimen for oral administration is suitably about 0.001 mg/Kg to 120 mg/Kg, of a compound of formula (1) or a pharmaceutically acceptable salt thereof calculated as the free base. The daily dosage regimen for parenteral administration is suitably about 0.001 mg/Kg to 40 mg/Kg, for example about 0.005 mg/Kg to 10 mg/Kg, of a compound of the formula (1) or a pharmaceutically acceptable salt thereof calculated as the free base. The active ingredient may be administered as required, for example from 1 to 8 times a day or by infusion. The compositions of the invention are bronchodilators and are useful in chronic reversible obstructive lung disease for example asthma and bronchitis. The compositions of the present invention have vasodilator activity and are of use in the treatment of angina, hypertension and congestive heart failure. Such conditions can be treated by administration orally, sublingually, topically, rectally, parenterally or by inhalation. For administration by inhalation dosages are controlled by a valve, are administered as required and for an adult are conveniently in the range 0.1-5.0 mg, of a compound of the formula (1) or a pharmaceutically acceptable salt thereof.

The compounds of this invention may be co-administered with other pharmaceutically active compounds, for example in combination, concurrently or sequentially. Conveniently the compounds of this invention and the other active compound or compounds are formulated in a single pharmaceutical composition. Examples of compounds which may be included in pharmaceutical compositions with the compounds of the formula (1) are bronchodilators such as sympathomimetic amines for example isoprenaline, isoetharine, salbutamol, phenylephrine and ephedrine or xanthine derivatives for example theophylline and aminophylline, anti-allergic agents for example disodium cromoglycate, histamine H₁-antagonists, vasodilators for example hydralazine, angiotensin converting enzyme inhibitors for example captopril, anti-anginal agents for example isosorbide nitrate, glyceryl trinitrate and pentaerythritol tetranitrate, anti-arrhythmic agents for example quinidine, procainamide and lignocaine, calcium antagonists for example verapamil and nifedipine, diuretics such as thiazides and related compounds for example bendrofluazide, chlorothiazide, chlorothalidone, hydrochlorothiazide, and other diuretics for example frusemide and triamterene, and sedatives for example nitrazepam, flurazepam and diazepam.

In another aspect the present invention provides a process for the preparation of compounds of the formula (1) and pharmaceutically acceptable salts thereof, which process comprises cyclising a compound of the formula (2) :

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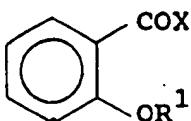
40 wherein R¹ is as hereinbefore defined, and R⁵ is a group R² as hereinbefore defined or a precursor thereof and thereafter where necessary :
 - converting a group R⁵ to a group R²;
 - optionally forming a pharmaceutically acceptable salt thereof.

45 Suitably the cyclisation of a compound of the formula (2) is performed in the presence of a base such as aqueous sodium hydroxide or potassium hydroxide optionally with a co-solvent such as pyridine, tetrahydrofuran, dioxane or dimethylformamide at ambient or elevated temperatures for example 20-150 °C, preferably at the reflux temperature of the reaction mixture.

An example of R⁵ being a precursor to a group R² is when R⁵ is a nitro group. Such a group can be converted to an amino group by treatment with a reducing agent, for example by catalytic hydrogenation.

50 A compound of the formula (1) wherein R² is amino can be converted to a C₁-4alkylamino group under reductive amination conditions, for example by reaction with a suitable aldehyde or ketone such as acetaldehyde or acetone in the presence of a reducing agent such as sodium borohydride, or by reaction with a suitable orthoformate such as trimethylorthoformate followed by reaction with a reducing agent such as sodium borohydride.

55 A compound of the formula (2) can be prepared by reaction of a compound of the formula (3) :

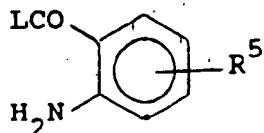


(3)

5

wherein X is halo, and R¹ is as hereinbefore defined, with a compound of the formula (4) :

10



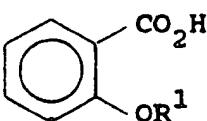
(4)

15 wherein L is amino or C₁-4 alkoxy and R⁵ is as hereinbefore defined, and thereafter, when L is C₁-4 alkoxy, by reaction with ammonia.

20 Suitably the reaction of compounds of the formulae (3) and (4) is performed at ambient or elevated temperature e.g. 20-100 °C in a solvent such as acetone, toluene or tetrahydrofuran in the presence of a base such as triethylamine, pyridine, aqueous sodium hydroxide or aqueous sodium acetate. Preferably the reaction is performed at ambient temperature in acetone or tetrahydrofuran in the presence of a mixture of acetic acid and aqueous sodium acetate. Suitably X is bromo or chloro.

A compound of the formula (3) can be prepared by reaction of a compound of the formula (5) :

25



(5)

30 wherein R¹ is as hereinbefore defined, with a suitable halogenating agent. Suitable halogenating agents include thionyl chloride or phosphorous tribromide.

Pharmaceutically acceptable base addition salts of the compounds of the formula (1) may be prepared by standard methods, for example by reacting a solution of the compound of the formula (1) with a solution of the base.

35 Pharmaceutically acceptable acid addition salts of the compounds of the formula (1) wherein R² is -NR³R⁴ may be prepared from the corresponding base of the compounds of the formula (1) in conventional manner. For example the base may be reacted with an acid in a C₁-4 alkanol, or an ion-exchange resin may be used. The salts of the compounds of the formula (1) may be interconverted using ion-exchange resins. Non-pharmaceutically acceptable salts are therefore of use as they can be converted to pharmaceutically acceptable salts.

40 In another aspect the present invention provides a compound of the formula (1) as hereinbefore defined or 2-(2-methoxyphenyl)quinazolin-4(3H)-one or a pharmaceutically salt thereof for use as a medicament, in particular for use as a bronchodilator and/or vasodilator.

45 In a further aspect the present invention provides the use of a compound of the formula (1) as hereinbefore defined, 2-(2-methoxyphenyl)quinazolin-4(3H)-one or 2-(2-ethoxyphenyl)quinazolin-4(3H)-one or a pharmaceutically salt thereof in the manufacture of a medicament having bronchodilator and/or vasodilator activity.

2-(2-Methoxyphenyl)quinazolin-4(3H)-one and 2-(2-ethoxyphenyl)quinazolin-4(3H)-one can form pharmaceutically acceptable salts, be formulated as pharmaceutical compositions and be used as medicaments as hereinbefore described for compounds of the formula (1).

50 The following biological test method, data and Examples serve to illustrate this invention.

Bronchodilatation - In vivo

55 Male guinea-pigs of the Dunkin Hartley strain (500 - 600g) were anaesthetised with Sagatal (pentobarbital sodium) (60 mg/kg). Airway resistance was measured using a modification of the classical Konzett-Rossler technique (Versuchsanordnung zu Untersuchungen an der Bronchialmuskulatur. Naunyn-Schmiedebergs Arch. Exp. Path. Pharmak., vol 195: pp 71-74, (1940)). U46619 (9,11-methanoepoxy-PGH₂)

was infused i.v. at a rate of 2.5 nmol/min, this produced a steady state of bronchoconstriction (approximately 120% increase from basal airway resistance). The compound under test was administered by i.v. bolus injection, and the subsequent peak inhibition of bronchoconstriction recorded.

5 Administration of the compound of Example 1 (10 μ mol/kg) reduced the U46619-induced bronchoconstriction by 34%. This result demonstrates in vivo anti-bronchoconstrictor activity.

Phosphodiesterase activity

10 The activity of the compounds of the present invention as inhibitors of a calmodulin insensitive cyclic GMP phosphodiesterase was measured using the procedure described in European Patent Application No. 293063. The compounds of Examples 1 to 5 had IC₅₀ values (the concentration of inhibitor required for 50% inhibition of enzyme activity) in the range 0.71 to 5.30 μ M. The compounds of the present invention have the advantage that they are selective in not inhibiting cyclic AMP phosphodiesterase (type III).

15

Example 1

20

2-(2-Propoxyphenyl)quinazolin-4(3H)-one

a) A mixture of 2-propoxybenzoic acid (5 g) in thionyl chloride (20 ml) was heated under reflux for three hours. Thionyl chloride was removed under reduced pressure and the residue was azeotroped with toluene to yield the acid chloride as a yellow oil (5.5 g). A solution of anthranilamide (3.77 g) in a mixture of saturated aqueous sodium acetate (20 ml) and acetic acid (20 ml) was added to the yellow oil in acetone (4 ml). The resulting solution was stirred at ambient temperature for one hour to yield as a light brown precipitate 2-(2-propoxybenzamido)benzamide, 3.78 g. A sample recrystallised from ether had m.p. 149-150 °C.

25 b) 2-(2-Propoxybenzamido)benzamide (2.73 g) was added to a refluxing mixture of 2 Normal aqueous sodium hydroxide (55 ml) and pyridine (2 ml). The resulting solution was stirred under reflux for 15 minutes and was then poured onto ice (150 ml) and acidified with concentrated hydrochloric acid to yield a sample of the title compound, 2.28 g, m.p. 88-89 °C. This together with another sample (0.77 g) similarly prepared was recrystallised from ethanol/water to yield the pure title compound as a white solid, 2.57 g, m.p. 89-90 °C.

40

Example 2

7-Methylthio-2-(2-propoxyphenyl)quinazolin-4(3H)-one

a) Methyl mercaptan was bubbled through a solution of copper sulphate pentahydrate (50 g) in water (200 ml) for 30 minutes to form cuprous thiomethoxide (11.70 g) as a precipitate, which was collected and washed successively with water, methanol and ether.

45 A solution of sodium nitrite (3.70 g) in water (15 ml) was added with cooling (3-4 °C) to a stirred suspension of 4-amino-2-nitrobenzoic acid (9.11 g) in water (50 ml) and concentrated sulphuric acid (10 ml) in order to prepare the diazonium salt. The resultant solution was added dropwise during 30 minutes to a cooled (4 °C) slurry of cuprous thiomethoxide (11.7 g) in water (20 ml) and the reaction mixture was stirred for 1.5 hours at ambient temperature.

50 The reaction mixture was extracted well with chloroform (a total of 650 ml) and the chloroform extracts were washed with 2 Normal hydrochloric acid (2 x 25 ml), dried (magnesium sulphate) and evaporated under reduced pressure to a residue. The residue was dissolved in dilute aqueous sodium hydroxide and 2 Normal hydrochloric acid was added to precipitate 4-methylthio-2-nitrobenzoic acid (3.71 g) m.p. 172.5 °C.

55 b) A stirred solution of 4-methylthio-2-nitrobenzoic acid (4.56 g) and thionyl chloride (2.77 g) in benzene (65 ml) was heated under reflux for 1.5 hours. Aqueous ammonia (10 ml) was added dropwise to the stirred cooled (<5 °C) reaction mixture, which was then stirred with cooling for 45 minutes. Benzene was removed

under reduced pressure and the residual solid was washed with water and recrystallised to yield 4-methylthio-2-nitrobenzamide, (2.30 g), m.p. 176.8 °C.

c) A stirred mixture of 4-methylthio-2-nitrobenzamide (2.47 g), stannous chloride dihydrate (13.13 g) and ethanol (90 ml) was heated under reflux under nitrogen for one hour. The reaction mixture was added to ice and neutralized to pH 7 with 5% aqueous sodium bicarbonate solution and the resultant mixture was extracted with ethyl acetate : methanol (9 : 1, 6 x 100 ml). The combined extracts were washed with brine, dried (magnesium sulphate) and evaporated under reduced pressure to yield 2-amino-4-methylthiobenzamide (1.84 g), m.p. 172.5-173.5 °C.

d) A solution of 2-propoxybenzoyl chloride (0.76 g) in acetonitrile (6 ml) was added dropwise to an ice-cold stirred mixture of 2-amino-4-methylthiobenzamide (0.70 g) and triethylamine (0.39 g) in acetonitrile (6 ml). The reaction mixture was stirred at ambient temperature for 17 hours. Acetonitrile was removed under reduced pressure and the residual solid was washed with water and recrystallised from ethanol to yield 4-methylthio-2-(2-propoxybenzamido)benzamide (0.49 g), m.p. 178.5-181 °C. A further sample (0.40 g, m.p. 182.4 °C) was prepared by evaporating the ethanolic mother liquor and recrystallising the residue from ethanol.

e) A stirred solution of 4-methylthio-2-(2-propoxybenzamido)benzamide (0.85 g) and pyridine (1 ml) in 2 Normal aqueous sodium hydroxide was heated under reflux for 2 hours. The cooled reaction mixture was acidified with concentrated hydrochloric acid and the resultant mixture was extracted with chloroform (3 x 25 ml). The combined extracts were washed with water and then brine, dried (magnesium sulphate) and evaporated under reduced pressure to yield a solid which was recrystallised from ethanol to yield the title compound, 0.61 g, m.p. 156.5-158.5 °C.

Example 3

25

7-Nitro-2-(2-Propoxyphenyl)-4(3H)-quinazolinone

30 Methyl 4-nitroanthranilate (2.0 g, prepared from 4-nitroanthranilic acid by treatment with dry HCl in refluxing methanol) was added to a solution of 2-propoxybenzoyl chloride (2.0 g) and triethylamine (1.0 g) in dry tetrahydrofuran (5 ml) at 0 °C. After stirring at room temperature for 60 minutes, water was added and the mixture partitioned between water and dichloromethane. The organic layer was separated, dried (magnesium sulphate) and evaporated to give a solid (3.6 g). This material (1.0 g) was dissolved in 50 ml of 35 saturated methanolic ammonia and the solution heated in a pressure vessel at 100 °C for 18 hours. Evaporation of the solvents and recrystallisation of the residue from dichloromethane-petroleum ether gave 7-nitro-(2-propoxyphenyl)-4(3H)-quinazolinone, 0.9 g, m.p. 138 °C.

40

Example 4

7-Amino-2-(2-Propoxyphenyl)-4(3H)-quinazolinone

45

A stirred solution of 7-nitro-2-(2-propoxyphenyl)-4(3H)-quinazolinone (3.0 g) in dry methanol (450 ml) was treated sequentially under a carbon dioxide atmosphere with 5% Pd/C (1.5 g) and anhydrous ammonium formate (2.8 g). After 60 minutes solids were removed by filtration and the filtrate evaporated to dryness. The residue was partitioned between water and dichloromethane, the organic layer separated, dried (magnesium sulphate) and evaporated. The residue was recrystallised from diethyl ether-petroleum ether to give 7-amino-2-(2-propoxyphenyl)-4(3H)-quinazolinone, 2.7 g, m.p. 185 °C.

Example 5

55

7-Methylamino-2-(2-Propoxyphenyl)-4(3H)-quinazolinone

7-amino-2-(2-propoxyphenyl)-4(3H)-quinazolinone (0.5 g) was heated under reflux in trimethylorthoformate (5 ml) for 22 hours. The reaction mixture was evaporated to dryness, the residue dissolved in dry tetrahydrofuran and treated with sodium borohydride (0.3 g) and 4A molecular sieves for 24 hours. The reaction mixture was partitioned between water and dichloromethane, the organic layer separated, dried (magnesium sulphate) and evaporated. The residue was recrystallised from dichloromethane-diethyl ether to give 7-methylamino-2-(2-propoxyphenyl)-4(3H)-quinazolinone 0.17 g, m.p. 204-205 °C.

Example 6

10

Pharmaceutical compositions for oral administration are prepared by combining the following :

15

	% w/w		
2-(2-Propoxyphenyl)quinazolin-4(3H)-one	0.5	3.0	7.14
2% w/w Soya lecithin in soya bean oil	90.45	88.2	84.41
Hydrogenated vegetable shortening and beeswax	9.05	8.8	8.45

20

The formulations are then filled into individual soft gelatin capsules.

25

Example 7

30

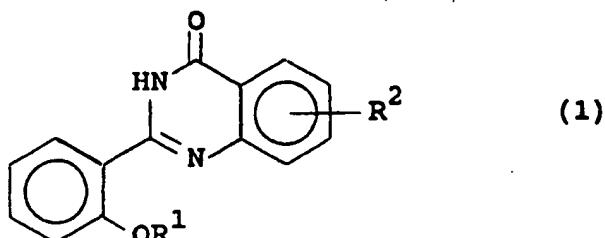
A pharmaceutical composition for parenteral administration is prepared by dissolving the title compound of Example 4 (0.02 g) in polyethylene glycol 300 (25 ml) with heating. This solution is then diluted with water for injections Ph. Eur. (to 100 ml). The solution is then sterilised by filtration through a 0.22 micron membrane filter and sealed in sterile containers.

Claims

35

1. A compound of the formula (1) :

40



45

or a pharmaceutically acceptable salt thereof, wherein

R¹ is C₁₋₆alkyl, C₂₋₆alkenyl, C₃₋₅cycloalkylC₁₋₄alkyl, phenylC₁₋₄alkyl or C₁₋₄alkyl substituted by 1 to 6 fluoro groups;

50

R² is hydrogen, C₁₋₆alkyl, C₁₋₆alkylthio, C₁₋₆alkoxy, nitro or -NR³R⁴; and

R³ and R⁴ are independently hydrogen or C₁₋₄alkyl optionally substituted by hydroxy provided that the carbon atom adjacent to the nitrogen atom is not substituted by hydroxy; with the proviso that R¹ is not methyl or ethyl when R² is hydrogen.

55

2. A compound according to claim 1 wherein R¹ is C₂₋₅alkyl.

3. A compound according to claim 1 wherein R¹ is or C₃₋₅alkenyl.

4. A compound according to any one of claims 1 to 3 wherein R² is hydrogen or C₁₋₆alkyl.

5. A compound according to any one of claims 1 to 3 wherein R² is C₁₋₆alkylthio or C₁₋₆alkoxy.

6. A compound according to any one of claims 1 to 3 wherein R² is nitro or -NR³R⁴.

7. A compound according to claim 1 which is
 2-(2-propoxyphenyl)quinazolin-4(3H)-one,
 7-methylthio-2-(2-propoxyphenyl)quinazolin-4(3H)-one,
 7-nitro-2-(2-propoxyphenyl)-4(3H)-quinazolinone,
 5 7-amino-2-(2-propoxyphenyl)-4(3H)-quinazolinone, or
 7-methylamino-2-(2-propoxyphenyl)-4(3H)-quinazolinone
 or a pharmaceutically acceptable salt thereof.

8. 2-(2-Methoxyphenyl)quinazolin-4(3H)-one or a compound according to any one of claims 1 to 7 or a pharmaceutically acceptable salt thereof, for use as a medicament.

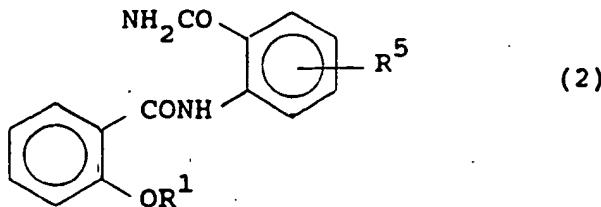
10. 9. A compound according to claim 8 for use as a bronchodilator and/or vasodilator.

10. A pharmaceutical composition which comprises a compound according to any one of claims 1 to 9 and a pharmaceutically acceptable carrier.

11. A process for preparing a compound of the formula (1) or a pharmaceutically acceptable salt thereof, as defined in claim 1 which process comprises cyclising a compound of the formula (2) :

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25 wherein R¹ is as defined in claim 1, and R⁵ is a group R² as defined in claim 1 or a precursor thereof, and thereafter where necessary :

- converting a group R⁵ to a group R²;
- optionally forming a pharmaceutically acceptable salt thereof.

30 12. A compound of the formula (2) as defined in claim 11.

35 13. The use of a compound of the formula (1) as defined in claim 1, 2-(2-methoxyphenyl)quinazolin-4(3H)-one or 2-(2-ethoxyphenyl)quinazolin-4(3H)-one or a pharmaceutically acceptable salt thereof in the manufacture of a medicament having bronchodilator and/or vasodilator activity.

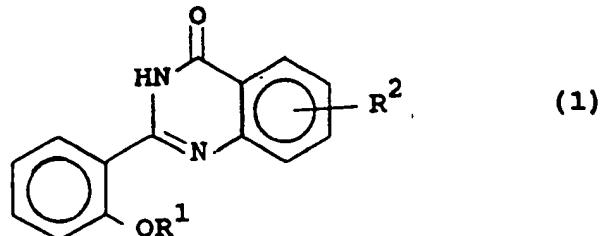
35 Claims for the following Contracting State: ES

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1. A process for preparing a compound of the formula (1) :

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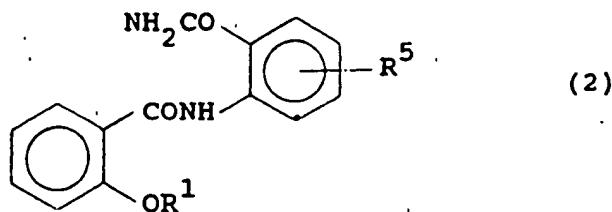


or a pharmaceutically acceptable salt thereof, wherein

R¹ is C₁-₆alkyl, C₂-₆alkenyl, C₃-₅cycloalkylC₁-₄alkyl, phenylC₁-₄alkyl or C₁-₄alkyl substituted by 1 to 6 fluoro groups;

50 R² is hydrogen, C₁-₆alkyl, C₁-₆alkylthio, C₁-₆alkoxy, nitro or -NR³R⁴; and
 R³ and R⁴ are independently hydrogen or C₁-₄alkyl optionally substituted by hydroxy provided that the carbon atom adjacent to the nitrogen atom is not substituted by hydroxy;
 with the proviso that R¹ is not methyl or ethyl when R² is hydrogen;
 which process comprises cyclising a compound of the formula (2) :

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10 wherein R¹ is as hereinbefore defined and R⁵ is a group R² as hereinbefore defined or a precursor thereof, and thereafter where necessary :

- converting a group R⁵ to a group R²;
- optionally forming a pharmaceutically acceptable salt thereof.

15 2. A process according to claim 1 for preparing a compound wherein R¹ is C₂-5alkyl.

3. A process according to claim 1 for preparing a compound wherein R¹ is C₃-5alkenyl.

4. A process according to any one of claims 1 to 3 for preparing a compound wherein R² is hydrogen or C₁-6alkyl.

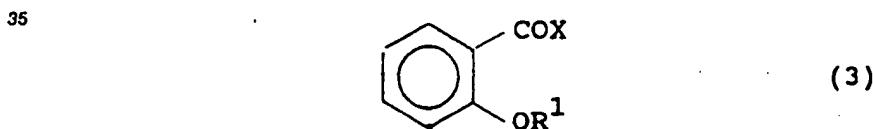
20 5. A process according to any one of claims 1 to 3 for preparing a compound wherein R² is C₁-6alkylthio or C₁-6alkoxy.

6. A process according to any one of claims 1 to 3 for preparing a compound wherein R² is nitro or -NR³R⁴.

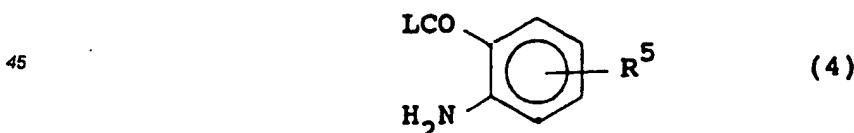
25 7. A process according to claim 1 for preparing a compound which is
2-(2-propoxypyhenyl)quinazolin-4(3H)-one,
7-methylthio-2-(2-propoxypyhenyl)quinazolin-4(3H)-one,
7-nitro-2-(2-propoxypyhenyl)-4(3H)-quinazolinone,
25 7-amino-2-(2-propoxypyhenyl)-4(3H)-quinazolinone, or
7-methylamino-2-(2-propoxypyhenyl)-4(3H)-quinazolinone
or a pharmaceutically acceptable salt thereof.

30 8. A process for preparing a pharmaceutical composition which comprises bringing into association a compound according to any one of claims 1 to 7 or 2-(2-methoxyphenyl)quinazolin-4(3H)-one and a pharmaceutically acceptable carrier.

9. A process for preparing a compound of the formula (2) as defined in claim 1 which comprises reacting a compound of the formula (3) :



40 wherein X is halo, and R¹ is as defined in claim 1 with a compound of the formula (4):

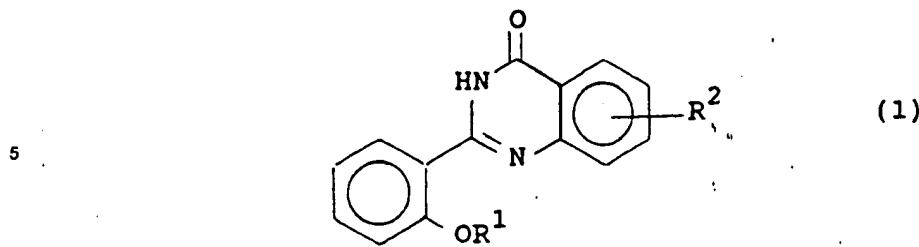


50 wherein L is amino or C₁-4alkoxy and R⁵ is as defined in claim 1, and thereafter, when L is C₁-4alkoxy, reacting with ammonia.

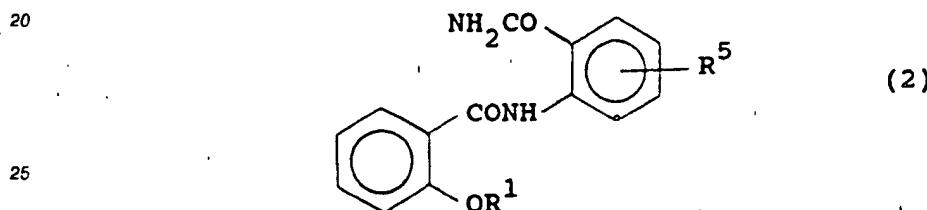
10. The use of a compound of the formula (1) as defined in claim 1, 2-(2-methoxyphenyl)quinazolin-4(3H)-one or 2-(2-ethoxyphenyl)quinazolin-4(3H)-one or a pharmaceutically acceptable salt thereof in the manufacture of a medicament having bronchodilator and/or vasodilator activity.

55 Claims for the following Contracting State: GR

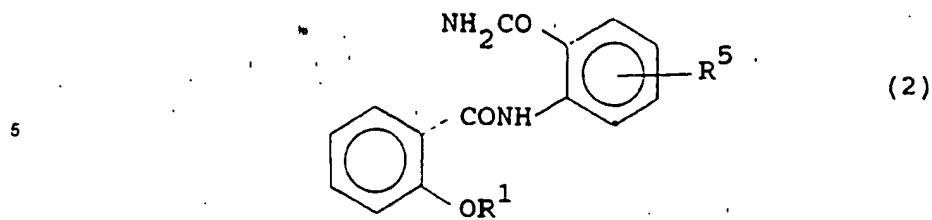
1. A process for preparing a compound of the formula (1) :



10 or a pharmaceutically acceptable salt thereof, wherein
 R¹ is C₁-₆alkyl, C₂-₅alkenyl, C₃-₅cycloalkylC₁-₄alkyl, phenylC₁-₄alkyl or C₁-₄alkyl substituted by 1 to 6
 fluoro groups;
 R² is hydrogen, C₁-₆alkyl, C₁-₆alkylthio, C₁-₆alkoxy, nitro or -NR³R⁴; and
 15 R³ and R⁴ are independently hydrogen or C₁-₄alkyl optionally substituted by hydroxy provided that the
 carbon atom adjacent to the nitrogen atom is not substituted by hydroxy;
 with the proviso that R¹ is not methyl or ethyl when R² is hydrogen;
 which process comprises cyclising a compound of the formula (2) :



25 wherein R¹ is as hereinbefore defined and R⁵ is a group R² as hereinbefore defined or a precursor thereof;
 and thereafter where necessary :
 30 • converting a group R⁵ to a group R²;
 • optionally forming a pharmaceutically acceptable salt thereof.
 2. A process according to claim 1 for preparing a compound wherein R¹ is C₂-₅alkyl.
 3. A process according to claim 1 for preparing a compound wherein R¹ is C₃-₅alkenyl.
 35 4. A process according to any one of claims 1 to 3 for preparing a compound wherein R² is hydrogen or C₁-₆alkyl.
 5. A process according to any one of claims 1 to 3 for preparing a compound wherein R² is C₁-₆alkylthio or C₁-₆alkoxy.
 6. A process according to any one of claims 1 to 3 for preparing a compound wherein R² is nitro or -NR³R⁴.
 40 7. A process according to claim 1 for preparing a compound which is
 2-(2-propoxyphenyl)quinazolin-4(3H)-one,
 7-methylthio-2-(2-propoxyphenyl)quinazolin-4(3H)-one,
 7-nitro-2-(2-propoxyphenyl)-4(3H)-quinazolinone,
 45 7-amino-2-(2-propoxyphenyl)-4(3H)-quinazolinone, or
 7-methylamino-2-(2-propoxyphenyl)-4(3H)-quinazolinone
 or a pharmaceutically acceptable salt thereof.
 8. A process for preparing a pharmaceutical composition which comprises bringing into association a
 compound according to any one of claims 1 to 7 or 2-(2-methoxyphenyl)quinazolin-4(3H)-one and a
 pharmaceutically acceptable carrier.
 50 9. A compound of the formula (2) :



10 wherein R¹ is as defined in claim 1, and R⁵ is a group R² as defined in claim 1 or a precursor thereof.

10. The use of a compound of the formula (1) as defined in claim 1, 2-(2-methoxyphenyl)quinazolin-4-(3H)-one or 2-(2-ethoxyphenyl)quinazolin-4(3H)-one or a pharmaceutically acceptable salt thereof in the manufacture of a medicament having bronchodilator and/or vasodilator activity.

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⑪ Publication number:

0 371 731 A3

⑫

EUROPEAN PATENT APPLICATION

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A61K 31/505

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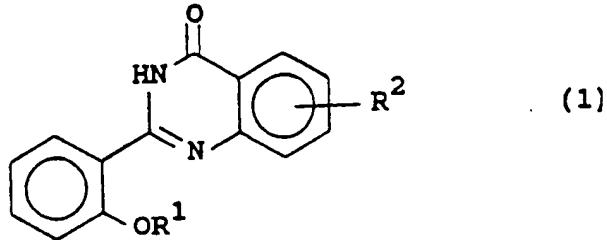
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⑯ Quinazolinone derivatives.

⑯ Compounds of the formula (1):



and pharmaceutically acceptable salts thereof are described wherein R¹ is C₁-₆alkyl, C₂-₆alkenyl, C₃-₅cycloalkylC₁-₄alkyl, phenylC₁-₄alkyl or C₁-₄alkyl substituted by 1 to 6 fluoro groups; R² is hydrogen, C₁-₆alkyl, C₁-₆alkylthio, C₁-₆alkoxy, nitro or -NR³R⁴; and R³ and R⁴ are independently hydrogen or C₁-₄alkyl optionally substituted by hydroxy provided that the carbon atom adjacent to the nitrogen atom is not substituted by hydroxy; with the proviso that R¹ is not methyl or ethyl when R² is hydrogen.

Processes for their preparation, pharmaceutical compositions containing them and their use as medicaments are described.

EP 0 371 731 A3



DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
D,Y	CHEMICAL ABSTRACTS, vol. 87, 1977, page 734, abstract no. 201571g, Columbus, Ohio, US; & JP-A-52 51 378 (CHUGAI PHARMACEUTICAL CO., LTD) 25-04-1977 "Abstract" - - - Y EP-A-0 058 822 (AMERICAN CYANAMID) "Pages 4-6; claims" - - - Y GB-A-1 523 081 (C. ERBA) "Pages 1,2,9; claims" - - - X TETRAHEDRON, vol. 29, 1973, pages 3173-3176, Pergamon Press Ltd; London, GB; G. SUBRAHMANYAM et al.: "Benzisoxazolium cations-II" "Page 3173; page 3174, column 2; page 3175 (nos. 7,6c)" - - - - -	1,2,4,8,10 1,2,4-6, 11 1,8-10,13 11,12	C 07 D 239/91 C 07 C 237/42 A 61 K 31/505
			TECHNICAL FIELDS SEARCHED (Int. Cl.5)
			C 07 D 239/00 C 07 C 237/00

The present search report has been drawn up for all claims

Place of search	Date of completion of search	Examiner
The Hague	18 October 90	FRANCOIS J.C.L.

CATEGORY OF CITED DOCUMENTS
X: particularly relevant if taken alone
Y: particularly relevant if combined with another document of the same category
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D: document cited in the application
L: document cited for other reasons
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&: member of the same patent family, corresponding document